Progress in Neuropsychopharmacology & Biological Psychiatry 77 (2017) 83–89

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Antidepressants and risk of dementia in migraine patients: A population-based case-control study

Cynthia Wei-Sheng Lee[a], Cheng-Li Lin[b,c], Pan-Yen Lin[d,e], Stephen Thielke[f], Kuan-Pin Su[d,e], Chia-Hung Kao[g,h,i,*]

[a] Center for Drug Abuse and Addiction, China Medical University Hospital, China Medical University, Taichung, Taiwan
[b] Management Office for Health Data, China Medical University Hospital, China Medical University, Taichung, Taiwan
[c] College of Medicine, China Medical University, Taichung, Taiwan
[d] Department of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan
[e] Graduate Institute of Neural and Cognitive Sciences, College of Medicine, China Medical University, Taichung, Taiwan
[f] Geriatric Research, Education, and Clinical Center, Puget Sound VA Medical Center, Seattle, WA, USA
[g] Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan
[h] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
[i] Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

ARTICLE INFO

Keywords:
Dementia
Antidepressants
SSRI
Tricyclic
Migraine
Case-control study

ABSTRACT

To ascertain the relationship between receipt of antidepressant agents and the risk of subsequent dementia in migraine patients. A population-based case-control analysis, using the Taiwan National Health Insurance Research Database. We identified 1774 patients with dementia and 1774 matched nondementia controls from migraine patients enrolled in the Taiwan National Health Insurance program between 2005 and 2011. The proportional distributions of exposure to three classes of antidepressant were compared between dementia and nondementia groups. Univariable and multivariable logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of dementia based on antidepressant exposure. The proportions of subjects taking tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and new-generation antidepressants (NGAs) in dementia versus nondementia groups are 52.3 vs 51.2%, 25.5 vs 30.7%, and 18.8 vs 6.26%, respectively. The adjusted ORs of dementia were 1.02 (95% CI = 0.89, 1.17; $P = 0.56$) for TCAs, 0.58 (95% CI = 0.50, 0.69; $P < 0.001$) for SSRIs, and 4.23 (95% CI = 3.34, 5.37; $P < 0.001$) for NGAs. Treatment with SSRIs was associated with a decreased risk of dementia in migraine patients. TCAs showed no association with dementia risk, and NGAs showed increased risk. Given the possibility of confounding by indication, additional prospective trials and basic research are needed before drawing conclusions about the population-level risks for dementia onset conferred by antidepressant medications.

1. Introduction

Patients with depression often show increasing cognitive impairment with recurring episodes (Kim et al., 2016). Late-life depression is consistently and similarly associated with a twofold increased risk of dementia (Cherbuin et al., 2015). Reciprocal and overlapping biological pathways might contribute to cognitive dysfunction in major depression, including an hyperactive hypothalamic-pituitary-adrenal axis, an increase in oxidative and nitrosative stress, inflammation (such as enhanced production of pro-inflammatory cytokines), mitochondrial dysfunction, increased apoptosis, and a diminished neurotrophic support (Carvalho et al., 2014). In Taiwan, migraine sufferers had a 1.33-fold higher risk of incident dementia compared to non-migraine controls (Chuang et al., 2013). The genetic background, an energy deficit, excitotoxicity, vascular and thrombotic properties can influence both migraine and dementia, resulting in a neuronal dysfunction, increased cellular vulnerability, neurodegeneration and ultimately cell death. A mechanism involved in the pathogenesis of these disorders is a metabolic disturbance of certain brain cells due to mitochondria dysfunction (Sas et al., 2010). Migraine preventive medications currently available in Taiwan can be categorized into β-blockers, antidepressants, calcium channel blockers, anticonvulsants, nonsteroid anti-inflammatory drugs, botulinum toxin type A and miscellaneous medications. Propranolol is recommended as the first-line medication

* Corresponding author at: Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan.
E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

http://dx.doi.org/10.1016/j.pnpbp.2017.04.006
Received 20 January 2017; Received in revised form 28 March 2017; Accepted 6 April 2017
Available online 07 April 2017
0278-5846/

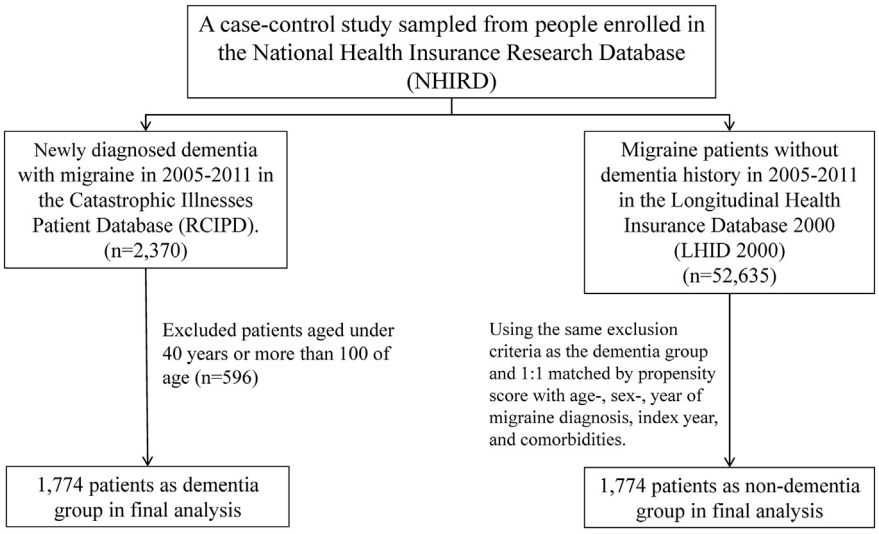

Fig. 1. The flow chart of study subjects' selection.

for migraine prevention. Valproic acid, topiramate, flunarizine and amitriptyline are suggested as the second-line medications. The rest medications are used when the above medications fail (Treatment guidelines for preventive treatment of migraine, 2008).

Antidepressants are commonly used for migraine prevention (Diener et al., 2015; Holroyd and Bendtsen, 2010). Previous research has found that antidepressants may influence risk of dementia, but most of this research involved either subjects with a diagnosis of depression (Lee et al., 2016; Kessing et al., 2011), or all people who were prescribed these medications regardless of indication (Wang et al., 2016; Kessing et al., 2009). Investigation in patients with depression showed that treatment with TCAs was associated with a reduced risk of dementia, whereas SSRIs and newer non-SSRI antidepressants was associated with an increased risk of dementia (Lee et al., 2016; Kessing et al., 2011). Research in elders enrolled in a depression screening study demonstrated that SSRI and non-SSRI users had significantly higher dementia risk than the nondepressed nonusers, while SSRIs users had a significantly higher dementia risk than non-users with severe depression (Wang et al., 2016). Another study revealed that continued long-term antidepressant treatment was associated with a reduced rate of dementia in persons who purchased antidepressants (Kessing et al., 2009). No research to date has explored the pharmacoepidemiology of incident dementia among migraine patients. To evaluate the possibility that antidepressant use modifies the risk of dementia in patients with migraine, we characterized the prior use of antidepressant medications among migraine patients with and without dementia in a large national research database.

2. Materials and methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program, launched in 1995, has provided medical care coverage to > 99% of the 23.7 million residents of Taiwan (National Health Insurance Research Database, Taiwan, 2015). The program's clinical data is deidentified and stored in the National Health Insurance Research Database (NHIRD). The details of the NHI program and NHIRD have been described in previous research studies (Lee et al., 2016; Peng et al., 2015). Patient diagnoses are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR1). The IRB also specifically waived the consent requirement.

2.2. Data availability statement

All data and related metadata were deposited in an appropriate public repository in the National Health Research Institutes (NHRI). The data on the study population that were obtained from the NHIRD (http://nhird.nhri.org.tw/en/index.html) are maintained in the NHIRD (http://nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established by the government. Only citizens of the Republic of China who fulfill the requirements of conducting research projects are eligible to apply for the NHIRD. The use of NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p=987) and related regulations of National Health Insurance Administration and NHRI, and an agreement must be signed by the applicant and his/her supervisor upon application submission. All applications are reviewed for approval of data release.

2.3. Subject selection

Data were extracted from two subsets of the NHIRD: 1) the Longitudinal Health Insurance Database 2000 (LHID 2000) and 2) the Registry of Catastrophic Illnesses Patient Database (RCIPD) (Lee et al., 2016; Peng et al., 2015). All subjects with migraine (ICD-9-CM code 346) constituted the base population (Fig. 1), from which cases and controls were selected. Cases were those subjects who, between 2005 and 2011, both were 40 years of age or older and had a new diagnosis of dementia (ICD-9-CM code 290). We include patients aged 40 to 65 years old in order to cover the cases of young-onset dementia. The dementia diagnosis date was defined as the index date. Control subjects came from the same base population, but did not have a diagnosis of dementia in LHID 2000. Individuals in both groups with incomplete information were excluded. The dementia cases and nondementia controls were selected at a ratio of 1:1 matching on propensity score (Parsons, 2004). The propensity score was calculated using logistic regression to estimate the probability of the dementia assignment given the baseline variables including age, sex, year of migraine diagnosis, the year of index date, and the comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), stroke (ICD-9-CM codes